PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Manual ventilation to prevent hypoxemia during endotracheal intubation of critically ill adults: protocol and statistical analysis plan for a multi-center randomized trial
AUTHORS	Casey, Jonathan; Janz, David; Russell, Derek; Vonderhaar, Derek; Joffe, AM; Dischert, Kevin; Brown, Ryan; Lester, Michael; Zouk, Aline; Gulati, Swati; Stigler, William; Rice, TW; Semler, Matthew

VERSION 1 – REVIEW

REVIEWER	Jarrod Mosier, MD University of Arizona, United States
REVIEW RETURNED	23-Apr-2018

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. This is important work as the optimal method of preventing desaturation and aspiration with airway management in the critically ill is paramount. I only have a couple of comments: 1. Minor point- "Millions" of critically ill patients don't get intubated every year. It certainly is thousands though: Pfunter A, Wier L, Stocks C. Most Frequent Procedures Performed in U.S. Hospitals, 2011. HCUP Statistical Brief #165. Agency for Healthcare Researcha dn Quality, Rockville, MD.2013. 2. Major point- There are so many variables with airway management in critically ill patients that unless you control for them, you will very likely not find any difference in your 400 patient sample size. For example, of all the variables that lead to desaturation (how obese are the patients, how are the patients preoxygenated, in what position are they preoxygenated, how severe is their airspace disease that reduces the efficacy of preoxygenation, was apneic oxygenation use, if so, what flow rate and device were used, what device was used to intubated, who did it, and how long did it take), failure to control for these will fail to uncover the true effect of the intervention despite a very well done multicenter randomized trial that will no doubt get published in a high impact journal. 3. I look forward to seeing your results!

REVIEWER	Messika, Jonathan Hôpital Louis Mourier, Colombes, France
REVIEW RETURNED	30-Apr-2018

GENERAL COMMENTS	This protocol aims in comparing two peri-intubation strategies. the authors and investigators ought to be commended for planning and performing this interesting study. Some details of importance should be added to this manuscript

	Major comments - My main concern lies on the design of the study. Do the patients in the "no prophylactic ventilation" group receive supplemental oxygen? *If so, and I personnaly think they should, in accordance with recent guidelines (Higgs et al, BJA 2018 Feb;120(2):323-352), the modality of apneic oxygenation should be detailed in the protocol, and eventually discussed in a discussion section that could be added. *If not, it's a huge flaw in the design of this study, and an ethical concern. In my point of view no equipoise exists if this arm does not receive supplemental oxygen . As recommended by Higgs et al (BJA 2018), peroxygenation should be the rule. Apneic oxygenation should be mantained as long as the airway is not intubated. The absence of peroxygenation would penalize this randomization arm. - Next, the inclusion and exclusion criteria are not excplicitly detailed, and this is another major point. The authors should add a specific part of the manuscript detailing the inclusion and exclusion criteria: is there a minimal SpO2 for inclusion? Can a very hypoxemic patient be included? Minor comments some minor precisions should be added in the intubation protocol: - are there any specific recommandations about the NMB used? - the reference that allowed to calculate the sample size is only cited in the online supplement; it should be cited in the main text (p19; L3). - the "best practices" training material should be added to the online material. It would allow to have a clearer view on the recommended procedures of the trial. Likewise, were there some recommandations for the "non-ventilated" group? - the type of device used for pre-oxygenation should be collected: NIV, facemask, high-flow nasal cannula; - the authors should state in their manuscript that the reasons for non-inclusion will be collected in order to report these data on a flow-chart diagram. I'll be happy to review a revised manuscript, if the authors consider they can answer my concerns.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:
Reviewer: 1, Jarrod Mosier, MD
1. Minor point- "Millions" of critically ill patients don't get intubated every year. It certainly is thousands though: Pfunter A, Wier L, Stocks C. Most Frequent Procedures Performed in U.S. Hospitals, 2011. HCUP Statistical Brief #165. Agency for Healthcare Researcha dn Quality, Rockville, MD.2013.

• We appreciate the reviewer's comment and his suggestion of this excellent epidemiological review quantifying the frequency of procedures in the United States. Table 1 in the referenced article suggests the number of patients undergoing "Respiratory intubation and mechanical ventilation" in the Unites States in 2011 was 1,635,000. To be conservative, we revised the sentence in our manuscript to state: "Hundreds of thousands critically ill adults require endotracheal intubation each year in the United States alone, but despite the frequency of this procedure, there are currently no high-quality data available to help providers understand the potential benefits and risks of providing prophylactic ventilation between induction and intubation," and we have referenced the suggested article.

2. Major point- There are so many variables with airway management in critically ill patients that unless you control for them, you will very likely not find any difference in your 400 patient sample size. For example, of all the variables that lead to desaturation (how obese are the patients, how are the patients preoxygenated, in what position are they preoxygenated, how severe is their airspace disease that reduces the efficacy of preoxygenation, was apneic oxygenation use, if so, what flow rate and device were used, what device was used to intubated, who did it, and how long did it take), failure to control for these will fail to uncover the true effect of the intervention despite a very well done multicenter randomized trial that will no doubt get published in a high impact journal.

- The reviewer raises an important concern about patient and operator factors beyond the study intervention that may contribute to variability in the outcome of lowest oxygen saturation during endotracheal intubation (e.g., body mass index, severity of illness, device selection). The concern would be that variation in such factors could introduce “noise” that masks the “signal”, whereby a tightly controlled explanatory trial in which every aspect of the procedure was similar between groups except the intervention would find the intervention effective, but the additional variation added by differences in patients and co-interventions in a pragmatic trial precludes identification of the intervention’s effect because the intervention influences only a small proportion of the overall variation in the outcome. We agree that controlling for such variation may be important. Generally, there are three approaches to controlling for variation: restricting, matching, or accounting. The reviewer suggests restricting the study population (e.g., perhaps enrolling only patients with a low BMI, a high severity of illness, or who are being intubated with a video laryngoscopy). This would have the advantage of controlling variability, but would then limit the generalizability of the findings to a restricted group of patients, operators, and devices. We propose to control for this variation by accounting rather than restricting. Specifically, we will include many of the factors that contribute to variation in the outcome in a multivariable model to understand the effect of the intervention on the outcome after holding constant severity of illness (APACHE II score), approach to pre-oxygenation, etc. Additionally, we propose an even more sophisticated approach to dealing with this important challenge: including a pre-specified analysis in which each individual intubation is assigned a predicted value for lowest oxygen saturation using a risk score which includes the exact types of patient, operator, and procedural factors that might influence oxygen saturation, and comparing the observed to expected lowest oxygen saturation for each patient in each group. This approach has the advantage of comparing patients between groups after accounting for all the variables that introduce variability into the risk of the primary outcome, and it is anticipated to increase the power to detect differences between groups that might be masked due to variation in other factors. The limitations of this approach are that it requires multivariable modeling and is more complex in its application than restriction. While the current protocol and statistical analysis plan does not have a natural section in which to detail the important discussion the reviewer raises, we have submitted a full separate manuscript describing the modeling of non-intervention risk factors for lowest oxygen saturation that we will be controlling for, which will be cited for readers at the time of publication of the results of the trial.

3. I look forward to seeing your results!

Reviewer: 2, J. Messika
Major comments
1. My main concern lies on the design of the study. Do the patients in the "no prophylactic ventilation" group receive supplemental oxygen? *If so, and I personnaly think they should, in accordance with recent guidelines (Higgs et al, BJA 2018 Feb;120(2):323-352), the modality of apneic oxygenation should be detailed in the protocol, and eventually discussed in a discussion section that could be added. *If not, it's a huge flaw in the design of this study, and an ethical concern. In my point of view no equipoise exists if this arm does not receive supplemental oxygen. As recommended by Higgs et

al (BJA 2018), peroxygenation should be the rule. Apneic oxygenation should be mantained as long as the airway is not intubated. The absence of peroxygenation would penalize this randomization arm.

- The trial protocol controls only management of ventilation between induction and laryngoscopy. It leaves the decision of whether or not to use apneic oxygen up to the clinical providers. Based on the preliminary data, approximately 80% of the patients in the “no prophylactic ventilation” group will receive apneic ventilation. The details of apneic oxygenation administration, including modality, are being prospectively collected and will be reported in the final manuscript. We felt it was safe to defer the decisions regarding apneic oxygenation to treating clinicians because we have previously conducted a randomized trial comparing apneic oxygenation to no apneic oxygenation in the same setting and study population as the current trial, and found no significant difference in lowest oxygen saturation with use of apneic oxygenation (Semler, et al. Randomized Trial of Apneic Oxygenation during Endotracheal Intubation of the Critically Ill. Am J Respir Crit Care Med. 2016 Feb 1;193(3):273-80). With this data from the same study setting demonstrating that mandating apneic oxygenation did not prevent complications, we felt safe allowing clinicians to make the decision whether or not to apply apneic oxygenation for the current study.

2. Next, the inclusion and exclusion criteria are not excplicitly detailed, and this is another major point. The authors should add a specific part of the manuscript detailing the inclusion and exclusion criteria: is there a minimal SpO2 for inclusion? Can a very hypoxemic patient be included?

- We appreciate the reviewer’s comments that the inclusion/exclusion criteria outlined in the population section were not sufficiently explicit. We have revised the manuscript to explicitly denote the inclusion and exclusion criteria and to note that there was no prespecified exclusion criteria based on baseline oxygen saturation.

Minor comments

Some minor precisions should be added in the intubation protocol:

1. Are there any specific recommandations about the NMB used?

- The trial protocol did not make any explicit recommendations on NMB use. In response to the reviewer’s comment above, we have made it clear that one of the inclusion criteria for the trial was “the planned procedural approach includes administration of an induction agent (with or without neuromuscular blockade).” We are prospectively collecting the use of NMB agent (including choice of agent and dose), and we will present the use of NMB by group. Based on preliminary data, we anticipate that more than 97% of patients will receive neuromuscular blockade.

2. The reference that allowed to calculate the sample size is only cited in the online supplement; it should be cited in the main text (p19; L3).

- As recommended by the reviewer, we included the name of the statistical software used to calculate the sample size in the main text

3. The "best practices" training material should be added to the online material. It would allow to have a clearer view on the recommended procedures of the trial. Likewise, were there some recommendations for the "non-ventilated" group?

- We appreciate the reviewer’s comments. We are in complete agreement that it would be ideal to include images of the “best practices” training material provided during provider training and on the randomization sheets. Unfortunately, the “best practices” training material used for the trial employed images from textbooks and review articles for which we do not have the copyright, precluding us from including them in the current submission. Based on the reviewer’s advice, we will begin the process of contacting the copyright owners for each image in hopes of being able to include them in the online supplement of the final trial publication. Short of providing the images, we provide in the manuscript a description of the “best practice” recommendations provided, and at the reviewer’s request, we have updated the manuscript to include the full instructions provided to the no prophylactic ventilation

group, which were: “reminders that apneic oxygenation is allowed, that non-invasive ventilation should be removed at induction, and that bag-valve-mask ventilation is allowed for oxygen saturation < 90%.”

4. The type of device used for pre-oxygenation should be collected: NIV, facemask, high-flow nasal cannula

- Thank you. We are collecting data on the type of pre-oxygenation provided, and this will be reported in the trial manuscript (see “data collection” section).

5. The authors should state in their manuscript that the reasons for non-inclusion will be collected in order to report these data on a flow-chart diagram.

- We appreciate the author’s suggestion. We have added the following statement in the “Population” section of the manuscript: “A patient flow-chart diagram describing the number of patients screened for the trial, the number excluded, and the reasons for exclusion, will be included in the manuscript reporting the results of the trial.”

FORMATTING AMENDMENTS (if any)
Required amendments will be listed here; please include these changes in your revised version:
- Kindly re-upload FIGURES with at least 300 dpi resolution.

- All figures will be re-uploaded with image resolution of 300 dpi

VERSION 2 – REVIEW

REVIEWER	Messika, Jonathan Hôpital Louis Mourier, Colombes, France
REVIEW RETURNED	14-Jun-2018

GENERAL COMMENTS	The authors have adequately answer to my comments. Nevertheless, I think they misunderstood my comment on the "best practices". I think a reminder of these "best practices" can be presented as a text, and I don't think it is necessary to report the images. The authors should be commended for running such an interesting trial, and I'm eager to read the result of their trial.